In This Issue

In Review: MAP Kinase-Interacting Kinases

PAGE 441

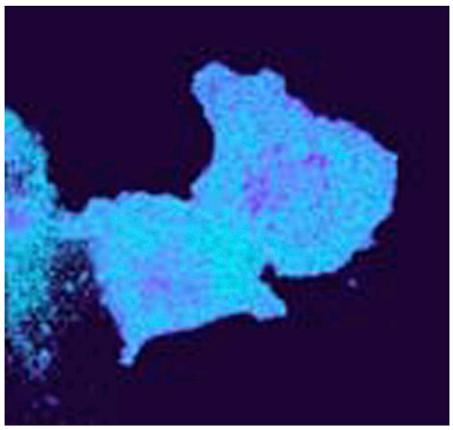
MAP kinase-interacting kinases (Mnks) are emerging as potential anticancer targets due to their critical roles in the protein synthesis. Diab et al. highlight the progress made in understanding their structures, functions, and clinical implications and propose strategies for designing pharmacological inhibitors.

In Brief: Modulating the Allosteric Function of the HER3 pseudokinase

PAGE 453

HER3 pseudokinase activates other human epidermal growth factor receptor tyrosine kinases and is a target of next-generation cancer drugs. Littlefield et al. analyze the interaction between HER3 and the kinase inhibitor bosutinib and suggest the potential to alter HER3 function with ATP-competitive compounds.

How Protein Kinase C Optimizes Its Signaling Range



PAGE 459

Antal et al. show that protein kinase C undergoes conformational changes upon phosphorylation-induced maturation in order to optimize its dynamic range of signaling. These conformational rearrangements keep the enzyme inactive under basal conditions but allow ultrasensitivity in responses to its activating ligand.

PA28αβ Acts as a Smart Sieve

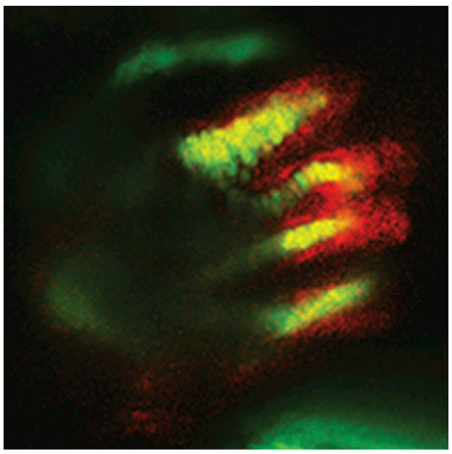
PAGE 470

PA28αβ is a proteasome activator involved in optimizing cytotoxic immunological responses; however, its precise mechanism of action is still unclear. Raule et al. discovered that PA28αβ reduces size and increases hydrophilicity of proteasome products, which is consistent with an unexpected ''smart'' sieve function.

NSAIDs with Antibacterial Activity

PAGE 481

Yin et al. describe the antibacterial activity of selected nonsteroidal anti-inflammatory drugs (NSAIDs) in vitro. The effects are linked to inhibition of DNA replication. The work suggests that NSAIDs have applications beyond their current use analgesic, fever-reducing, and anti-inflammatory agents.



Nitric Oxide Signaling in Craniofacial Development

PAGE 488

Kong et al. apply chemical genetics toward the study of neural crest cells and craniofacial morphogenesis and demonstrate that nitric oxide signaling and histone acetylation are coordinated mechanisms that regulate neural crest patterning, differentiation, and convergence during craniofacial development.

In This Issue

Tools for Digging Deeper into the Natural Products' Goldmine

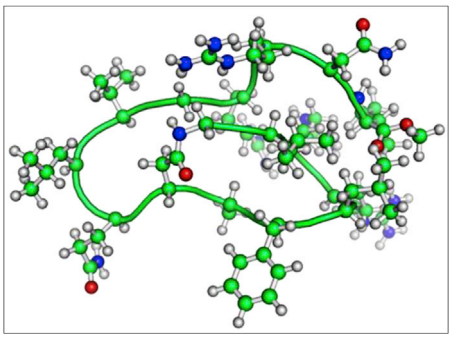
PAGE 502

Although fungi produce many natural products, most of their biosynthetic pathways appear silent. As a proof of concept, Unkles et al. express the entire penicillin biosynthesis pathway in a heterologous host by combining improved yeast cloning technology, polycistronic mRNA, and viral 2A peptide sequences.

Putting a Lasso around *Mycobacterium tuberculosis*

PAGE 509

Gavrish et al. screen uncultured actinomycetes for mycobacteria-specific compounds and discover lassomycin, which kills both growing and dormant *M. tuberculosis*. Lassomycin is a ribosomally encoded cyclic peptide that activates the ClpC1 ATPase without stimulating proteolysis by the ClpP1P2C1 protease complex.



Biosynthesis of the Yanuthone D

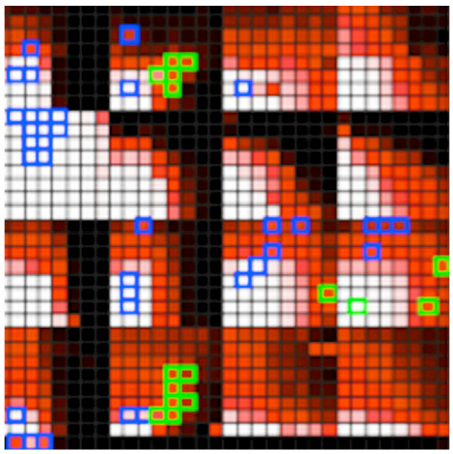
PAGE 519

In *Aspergillus niger*, 6-MSA is a precursor to the antifungal compound yanuthone D. Holm et al. show that yanuthone D is formed via 8 biosynthetic steps using 10 enzymes encoded by the *yan* gene cluster, including O-mevalon transferase. The authors also identify an additional class of yanuthones.

From Zebrafish to Inhibitors of the Wnt/β-Catenin Pathway

PAGE 530

Nishiya et al. develop a chemical suppressor screening system for anticancer drug candidates that target Wnt/β-catenin pathway using zebrafish as a model. The system does not require genotyping and large-scale fish facilities and may provide opportunities for phenotype-based screening to small-scale laboratories.



Suppressive Antifungal Drug Interactions and Their Networks

PAGE 541

Although knowledge of drug suppression is vital to avoid efficacy reducing drug interactions, drug-drug suppression relationships have not been systematically mapped. Cokol et al. identify 94 suppressive antifungal drug pairs and analyze the resulting suppression drug interaction network.

Structural Basis for Carrier Protein Posttranslational Modification

PAGE 552

Tufar et al. describe a crystal structure of PCP/Sfp complex that gives new insights into the mechanism of the phosphopantetheine transfer onto carrier proteins. Hydrophobic contacts and an intermolecular hydrogen bond, which seem to be conserved in many organisms, are the driving force of the complex formation.